said composition not being a dispersion.

REMARKS

Claim 58 has been amended for clarity by further defining relative bioavailability as relative to a control composition, in parallel with the control defined in other independent claims. Support is found in the specification, for example at page 1, lines 8-10, at page 7, lines 26-29, and in other independent claims (e.g., see independent claims 1, 30, and 86, for example).

Attached to this response are pages captioned "Version Marked Up To Show Changes Made", which identify the exact nature of the amendments.

Claims 1-155 continue to stand rejected under 35 USC 103(a) as being unpatentable over Piergiorgio et al., US 4,880,623. Piergiorgio et al. disclose a sustained release composition of nifedipine. Pending claim 1 of the instant application distinguishes over Piergiorgio et al. because claim 1 requires a drug in a solubility-improved form combined with a concentration-enhancing polymer, the polymer being present in a sufficient amount to provide

> "a maximum concentration of said drug in said use environment that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug in said use environment that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration."

In the office action, the Examiner sustained the rejection, arguing that applicants provided no data showing that the polymers disclosed and taught by Piergiorgio would not enhance drug concentration. It is Applicants' position that such a showing is provided by Piergiorgio itself, however. That is, in the examples of Piergiorgio et al., the dose-normalized maximum drug concentration (C_{max}) and AUC in the blood decreased with the addition of the polymer. This is exactly contrary to the claimed invention, which requires the addition of a concentration-enhancing polymer to a solubility-improved form of a drug to improve drug concentration relative to a control containing the same amount

of drug in the same solubility-improved form but that does not have the concentration-enhancing polymer.

Piergiorgio et al. disclose that polyethylene glycol may be used to wet the surface of an inert microparticle (such as lactose) to form granules containing small drug crystals. (Col. 2, lines 19-29). The granules may then be mixed with conventional excipients suitable for the manufacture of the desired solid dosage forms, such as substances which swell and then dissolve when in contact with GI juices to prolong a "retardant effect." Col. 3, lines 10-14. Such substances include hydroxypropylmethylcellulose (HPMC), methylcellulose, hydroxypropylcellulose, carboxyvinyl polymers, and xanthan gum. Col. 3, lines 15-17.

Piergiorgio et al. disclose *in vivo* studies with tablets made with and without HPMC. However, in contrast to the claims of the instant application, the tablets formed by Piergiorgio et al. with HPMC yielded lower dose-normalized maximum drug concentrations in the blood and lower AUCs than tablets formed with HPMC. Unfortunately, Piergiorgio et al. do not use the same amount of drug in the tablets tested in the examples. Thus, in order to compare the performance of the tablets containing HPMC with the performance of the tablets without HPMC, it is necessary to compare performance on a dose-normalized basis. While the absolute values for maximum drug concentration and AUC are higher for the tablets formed with HPMC (presumably due to the increase in amount of drug dosed), these absolute values are less than what would be expected on a dose-normalized basis.

For the tablets of Ex. 1 of Piergiorgio et al. containing 20 mg of Nifedipine, with no additional polymer, *in vivo* studies showed a C_{max} of 40.9 ng/ml, and an $AUC_{0-\infty}$ of 423.3 ng/ml x h. See Ex. 6, Table 2.

For the tablets of Ex. 2 of Piergiorgio et al. containing 40 mg of Nifedipine and HPMC, *in vivo* studies showed a C_{max} of 62.6 ng/ml, and an $AUC_{0-\infty}$ of 697.9 ng/ml x h. See Ex. 7, Table 2A.

However, comparing the tablets of Ex. 1 with the tablets of Ex. 2, the addition of HPMC did not result in improvement in the concentration in the blood of nifedipine. Although the dose of nifedipine was doubled in Ex. 2 relative to the dose of Ex. 1, the C_{max} only increased by 1.5, while the $AUC_{0-\infty}$ only increased by 1.6. On a dose-normalized basis, Ex. 1 had a C_{max}/mg of 2.05 (ng/ml)/mg, while Ex. 2 had a C_{max}/mg of 1.57 (ng/ml)/mg. Similarly, on a dose-normalized basis, Ex. 1 had an $AUC_{0-\infty}$/mg of 21.2 (ng/ml x h)/mg, while Ex. 2 had an $AUC_{0-\infty}$/mg of 17.5 (ng/ml x h)/mg.

Thus, on a dose-normalized basis, the C_{max} and $AUC_{0-\infty}$ decreased with the addition of the polymer. This is exactly contrary to the claimed invention, which requires the addition of the concentration-enhancing polymer to improve drug concentration and bioavailability relative to a control that does not have the concentration-enhancing polymer but contains the same quantity of drug.

Claim 1 is therefore not obvious in view of Piergiorgio et al. because Piergiorgio et al. does not teach the invention as a whole, which is the recognition that improved drug concentration in a use environment may be achieved by combining a drug in a solubility improved form with a sufficient amount of concentration-enhancing polymer. The use of a drug in a solubility-improved form provides the initially enhanced drug concentration in the use environment. Application, page 15 line 26 - page 16, line 27. The problem with using a solubility-improved form alone is that the initially enhanced drug concentration provided by the solubility-improved form often rapidly decreases to the equilibrium concentration due to the rapid precipitation or crystallization of the drug. Id. However, the inventors recognized that the initially enhanced concentration of the drug in the use environment provided by a drug in a solubility-improved form could be maintained, and in some cases enhanced, by retarding precipitation, crystallization, or conversion of the drug to lower solubility forms through the use of a concentration-enhancing polymer. Thus, without implying any particular mechanism of action, it is believed that the concentration-enhancing polymers of this invention may be viewed as acting as crystallization or precipitation inhibitors. Surprisingly, this may be accomplished by simply combining the concentration-enhancing polymer with the drug in the solubility-improved form. Piergiorgio et al. do not teach or recognize the use of concentration-enhancing polymers to act as crystallization or precipitation inhibitors to maintain the initially enhanced drug concentration provided by a solubility-improved form of a drug.

Piergiorgio et al. may not have achieved increased drug concentration for either of two reasons. First, the drug in Piergiorgio et al. may not be in a solubility-improved form. The present application states that a solubility-improved form of the drug is a form which achieves a drug concentration in the use environment that is higher than the equilibrium concentration. Examples of solubility-improved forms include amorphous drug, highly soluble salt forms, and high-energy forms such as polymorphs. Page 9, lines 19-24. The drug in Piergiorgio et al. does not appear to be in any of these three forms.

Another type of solubility-improved form is a drug combined with a solubilizing agent. Page 9, line 25-26. The Examiner apparently takes the position that polyethylene glycol is a solubilizer. However, Piergiorgio et al. state that the polyethylene glycol is used to wet the surface of the inert excipient so that the solution of nifedipine will spread over the inert excipient and form tiny crystals when the solvent evaporates. Col. 2, lines 19-26. It does not appear that nifedipine has substantial solubility in polyethylene glycol, since Piergiorgio et al state that nifedipine precipitates from a solution of polyethylene glycol and solvent when the solvent is removed.

The second reason that Piergiorgio et al may not achieve concentration enhancement is that Piergiorgio et al. may not use enough polymer. It is noted that in Example 2 of Piergiorgio et al., the ratio of the nifedipine to HPMC appears to be about 3.5. (Col. 4, lines 27-68). In the instant application, for some drug/polymer combinations, it was necessary to have a ratio of drug to polymer of at least 3 in order to achieve a maximum drug concentration that was at least 1.25-fold that provided by the control. See, e.g., Example 1 at page 55, summarized in Table 1.2. (However, other drug/polymer combinations in the application needed less polymer, achieving a maximum drug concentration that was at least 1.25-fold that provided by the control at drug to polymer ratios of 20. See Example 5 at page 58, summarized in Table 3.) In any event, the examples of the instant application show that concentration-enhancement is a function of the amount of polymer present, and that to maximize the concentration-enhancement, a sufficient amount of polymer must be present. Page 58, lines 16-19.

In sum, the examples of Piergiorgio et al. strongly suggest that addition of HPMC would decrease drug concentration in a use environment. Accordingly, claim 1 patentably distinguishes over Piergiorgio et al. because the composition of Piergiorgio et al. does not achieve a concentration of the drug in a use environment that is improved relative to a control composition that contains an equivalent amount of drug in the solubility-improved form but that is free from the concentration-enhancing polymer.

Claims 2-37 depend from claim 1 and patentably distinguish over Piergiorgio et al. for the same reasons.

In addition, several of the dependent claims distinguish over Piergiorgio et al.

In claim 2, the solubility-improved form of the drug is a crystalline highly soluble salt form of the drug. In contrast, Piergiorgio et al. does not teach or suggest using highly soluble salt forms of nifedipine to improve drug concentration.

In claim 3, the solubility-improved form of the drug is a high-energy crystalline form of the drug, such as a polymorph. In contrast, Piergiorgio et al. does not teach or suggest using high energy forms of nifedipine to improve drug concentration.

In claim 4, the solubility-improved form of the drug is the amorphous form of the drug. In contrast, Piergiorgio et al. does not teach or suggest using the amorphous form of nifedipine to improve drug concentration, but instead states that the drug is in the form of "tiny" crystals. Col. 2, line 24.

In claim 7, the solubility-improved form of the drug is crystalline drug mixed with a solubilizer, the solubilzer being a pH control agent such as an acid or base. In claim 8, the solubilizer is selected from a group or organic acids. In contrast, Piergiorgio et al. does not teach or suggest using such solubilizers to improve drug concentration.

In claim 9, the solubility-improved form of the drug is a solution of drug substantially dissolved in a liquid to a concentration that is at least 10-fold said equilibrium concentration of said drug in said use environment. In contrast, Piergiorgio et al. teaches forming a solid drug composition, and does not teach or suggest using a solution of drug to improve drug concentration.

Claim 28 patentably distinguishes over Piergiogio et al. by requiring the composition to provide a maximum concentration in said use environment that is at least 1.25-fold the maximum drug concentration in said use environment provided by said control composition. As described above, the tablets of Piergiorgio et al. containing the polymer do not improve drug concentration relative to tablets that are free from the polymer.

Independent claim 30 is similar to claim 1, but requires the composition to provide a dissolution area under the concentration versus time curve in said use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition. Claim 30 thus distinguishes over Piergiorgio et al. for the same reasons as described above in connection with claim 1, since Piergiorgio et al. do not show enhanced drug concentration with the addition of the polymer.

Claims 31-57 are dependent from claim 30, and distinguish over Piergiorgio et al. for the same reason as claim 30.

Claims 31-34, and 36-38 are similar to claims 2-4 and 7-9, and distinguish over Piergiorgio et al. for the same reasons as described above in connection with claims 2-4 and 7-9.

Independent claim 58 requires the composition to provide a relative bioavailability of at least 1.25 relative to a control composition that is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form. As described above in connection with claims 1 and 30, the addition of the polymer in Piergiorgio et al. did not improve the relative bioavailability of the composition relative to the composition that did not contain the polymer. Claim 58 thus patentably distinguishes over Piergiorgio et al.

Claims 59-85 depend from claim 58, and therefore patentably distinguish over Piergiorgio et al. for the same reason as claim 58.

Claims 59-61 and 64-66 are similar to claims 2-4 and 7-9, and distinguish over Piergiorgio et al. for the same reasons as described above in connection with claims 2-4 and 7-9.

Claim 86 is a method claim that corresponds generally to the composition of claim 1. Claim 86 distinguishes over Piergiorgio et al. for the same reasons as described above in connection with claim 1.

Claims 87-105 are dependent from claim 86, and distinguish over Piergiorgio et al. for the same reasons as described above in connection with claim 86.

Claim 106 is a method claim that corresponds generally to the composition of claim 30. Claim 106 distinguishes over Piergiorgio et al. for the same reasons as described above in connection with claim 30.

Claims 107-125 are dependent from claim 106, and distinguish over Piergiorgio et al. for the same reasons as described above in connection with claim 106.

Claim 126 is a method claim that corresponds generally to the composition of claim 58. Claim 126 distinguishes over Piergiorgio et al. for the same reasons as described above in connection with claim 58.

Claims 127-145 are dependent from claim 126, and distinguish over Piergiorgio et al. for the same reasons as described above in connection with claim 126.

Claim 146 is an independent claim to a solution formed by administering a solid drug and a concentration enhancing polymer to a use environment. At least a portion of the dissolved drug is associated with at least a portion of the polymer in a plurality of assemblies of drug and polymer, the assemblies having a size of from about 10 to 1000

nanometers. Claim 146 distinguishes over Piergiorgio et al. for the same reasons as described above in connection with claim 1.

Claims 147-154 are dependent from claim 146 and distinguish over Piergiorgio et al. for the same reasons as described above in connection with claim 146.

Claim 155 is similar to claim 146 but contains the additional limitation that the polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate terephthalate and cellulose acetate isophthalate. None of these polymers are disclosed by Piergiorgio et al. Claim 155 distinguishes over Piergiorgio et al. for the same reasons as described above in connection with claim 146.

In view of the above comments, it is respectfully requested that the Examiner reconsider the rejection over Piergiorgio, and that the rejection be withdrawn. As stated above, Piergiorgio does not teach the invention as a whole. Nor does Piergiorgio provide any basis or motivation to make any modification needed to arrive at the claimed invention, and obviousness of an invention cannot be established absent some teaching, suggestion, or incentive supporting the modification. In re Napier, 34 USPQ2d 1782, 1784 (Fed. Cir., 1995). Even given that the prior art could be modified, that would not make the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Clearly, as Applicants have abundantly demonstrated by the traversal presented above, Piergiogio, absent hindsight, simply does not teach or suggest Applicants' invention.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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VERSION MARKED UP TO SHOW CHANGES MADE

Claim 58 has been amended as follows:

58. A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form; and

(b) a concentration-enhancing polymer combined with said drug in a sufficient amount so that said composition provides, after introduction to a use environment, a relative bioavailability of at least 1.25 relative to a control composition that is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form,

said composition not being a dispersions.